Remarks

Claims 39, 45, 70, 81 and 82 have been amended for clarification with respect to the comments provided by the Examiner in the Advisory Action dated December 20, 2005 and to put the claims in better form for allowance. No new matter has been added. Support for these amendments can be found throughout the instant specification. For example, support for the amendment to claim 70 can be found at page 15, lines 16 - 17. To advance prosecution of the instant specification and simplify current issues, claims 71-80 have been canceled. Applicants retain the right to present this subject matter in a continuing application.

Rejection Under 35 U.S.C. § 103(a)

In the Office Communication dated July 26, 2005, the Examiner has rejected claims 39-50, 52-82 and 84-92 under 35 U.S.C. § 103(a) as allegedly being obvious in view of the Portner and Märkl reference. The Examiner contends that it would have been obvious to one skilled in the art to supply air to the dialysis fluid of the instant invention because Figure 3b of the Portner and Märkl reference describes air being supplied to the dialyzing chamber.

A *prima facie* case of obviousness can only be established where there is some teaching of the prior art to produce the instant invention. As the Examiner points out, the Portner and Märkl reference discloses that when cells are pumped through the external module, the cells can suffer from oxygen limitation (page 404). The reference suggests this was one of the reasons persons skilled in the art abandoned the two-vessel dialysis reactor approach and turned to the alternative single-vessel dialysis reactor. Furthermore, the Portner and Märkl reference is a mini-review that supports the view that the field "as a whole" abandoned the two-vessel strategy and moved toward the single-vessel reactor. The prior art reference provides historical evidence that the field turned away from the two-vessel reactor by

showing the desirability of single-vessel reactor. The reference describes reasons why the two-vessel approach had been abandoned by the field and, thus, in teaching away from the present invention clearly fails to establish a *prima facie* case of obviousness.

Prima facie obviousness does not exist without some reason given in the prior art as to why one of ordinary skill in the art would have been prompted to make such a modification. No such reason exists in the Portner and Märkl reference. Air is supplied to the dialyzing chamber of Figure 3b for the sole purpose of avoiding disrupting cell adhesion to the fixed bed. Pumping air directly into the culture chamber of Figure 3b would create turbulence that would compromise cell adhesion to the fixed bed and therefore is not analogous art to the claimed invention. Instead, if supplying air to the dialysis chamber with the intent to maximize gas supply to free-floating cells had been the motivation for doing so in Figure 3b, then Figure 3a would be expected to show gas being pumped into the dialysis chamber and the culture chamber. Figure 3a clearly does not show this in the diagram nor is it contemplated in the text. Indeed, nowhere in the entire review article is there a description or a suggestion to supply air to culture chamber and the dialysis chamber. Simply supplying gas to the dialysis container of a two-vessel reactor would not enhance oxygen levels to the cultured cells. More likely than not, oxygen levels would be compromised severely because the oxygen must pass through the dialysis membrane to reach the cells. Supplying oxygen to the dialysis chamber would only be anticipated to have value in a one-chamber reactor where the surface volume of the dialysis membrane is much larger and there is no distance between the dialysis and culturing chambers. When the prior art itself provides no apparent reason to make the modification, the claimed subject matter of the instant application cannot be deemed to have been obvious.

In the Advisory Action dated December 20, 2005, the Examiner maintains the 35 U.S.C. § 103(a) rejection alleging it would have been obvious to supply air to the module of the instant invention since Portner and Märkl describe supplying oxygen to the culture vessel. Indeed, supplying gas to a culture fluid in a culture vessel is

obvious to those skilled in the art and in fact is practiced by those skilled in the art. This fact by itself provides no assistance to those seeking to solve the oxygen limitations of a two-vessel reactor that already has oxygen supplied to the culture vessel. The single-vessel reactor of Figure 3 is not analogous to a two-vessel reactor, indeed, the single-vessel reactor does not even suffer from the oxygen limitations imposed by the structural features of the two-vessel reactor. The single-vessel reactor has a single dialysis membrane in direct contact with the entire volume of dialysis and culture fluid. The two-vessel reactor has a confined membrane module physically removed from the dialysis and culture fluids. Contact of the dialysis and culture fluids are maintained by respective supply and discharge lines. It would not have been obvious to supply gas to a space so constricted in dimensions and fluid volume in order to solve the problem of oxygen limitation. The Portner and Märkl reference, although well aware of the limitations of a two-vessel reactor, provides no suggestion or teaching of how to overcome this limitation but merely points out that it is a limitation. Instead, the reference leads the artisan away from the two-vessel reactor by describing how the field "as a whole" abandoned the two-vessel approach. Absent any suggestion or teaching of introdrucing gas into the confined spaces of the membrane module, the Portner and Märkl reference cannot be used as support for this obviousness rejection.

The membrane module of the two-vessel reactor presents technical considerations distinct from the single-vessel reactor. As described in the instant specification (beginning on page 1, line 31), incorporating a dialysis membrane directly into the culture space limits large-scale production. Because dialysis membranes must have very low wall thickness to accommodate high dialysis capacity, they have limited mechanical strength thereby imposing capacity limitations on the single-vessel reactor. A two-vessel reactor circumvents this problem by utilizing a membrane module that is physically separated from the container for dialysis fluid and the culture vessel. Thus, the size of the dialysis container and culture vessel are no longer limited by the mechanical strength of the dialysis membrane. However, this solution involves new problems that the instant invention

solves. Consequently, the two-vessel reactor has different applications and technical considerations distinct from the one-vessel reactor.

Accordingly, a *prima facie* case of obviousness has not been established in view of the Portner and Märkl reference. Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

In view of the amendment and associated Remarks reconsideration and withdrawal of all outstanding rejections are deemed proper.

Applicants respectfully submit that the application is now in condition for allowance and request notice thereof.

Respectfully submitted,

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